UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/144,838	08/31/98	SIANI	M GRFN-020/01U

EXAMINER

HM12/0910

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ART UNIT	PAPER NUMBER
1627	25

DATE MAILED: 09/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

file copy

Advisory Action

Application No.	Applicant(s)
09/144,838	Siani et al.
Examiner	**Art Unit**
Bennett Celsa	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED _____ FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Aug 10, 2001*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search. (See NOTE below);

(b) ☒ they raise the issue of new matter. (See NOTE below);

(c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: *see attached*

4. ☐ Applicant's reply has overcome the following rejection(s):

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because:

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: *28-36*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

11. ☐ Other:

Advisory Action Cont.

***Additional Reasons for Non-entry of the After Final Amendment*:**

a. Applicant's proposed specification amendment necessitates the making of a new ground of rejection or objection e.g. objection for incomplete Application serial number which fails to specify the series of application e.g. 07/ or 08/ or 09/ .

b. Applicant's amendment of claim 28 necessitates the making of a new ground of rejection under 35 USC 112, second paragraph e.g. for lack of antecedent basis: see line 9 and "said first *parent* protein".

c. Applicant's amendment of claims 33 and 34 (e.g. changing "parent" to "families of") raises the issue of new matter.

d. Applicant's amendment of claims 33 and 34 (e.g. changing "parent" to "families of") which results in a change of scope necessitates additional consideration.

e. Applicant's amendment of claims 33 and 34 (e.g. changing "parent" to "families of") which results in a change of scope necessitates additional search.

f. Applicant's amendment of claims 33 and 34 (e.g. changing "parent" to "families of") which results in a change of scope may necessitate a new search, a new rejection and/or modification of present rejections of record in order to address the new claim limitation.

g. There is no reason why the amendment was not earlier presented.

h. The amendment does not materially reduce issues for appeal.

Brief Discussion of Outstanding Objection and/or Rejections in light of applicant's response in order to facilitate further prosecution of the present application.

1. Objection to the specification (e.g. docket number and improper serial number). This rejection is still outstanding pending an amendment which properly recites the intended serial number.

2. Indefinite rejection (e.g. ambiguous relative terms "first" and "second" protein and lack of standard) is maintained. There is nothing (e.g. amino acid composition, length or properties) given to distinguish the "first"from the "second protein" . Indeed applicant's method is clearly applicable to combining modules from the same or different proteins (E.g. see after-final response page 6, first full paragraph). Accordingly, the claimed language is clearly indefinite.

3. Indefinite rejection (e.g. claim 30: "parent protein molecules are of the same family of protein molecules"). Applicant's prior claim or proposed unentered amendment fails to address the crux of this rejection e.g.. what characteristics (e.g. chemical, structure, conformational etc) distinguishes one "family" of proteins from another. Accordingly, this rejection is maintained.

4. Indefinite rejection (e.g. claim 28 preamble as compared to claim 32 for a library) for inconsistency or confusion; upon further consideration is hereby withdrawn.

5. Indefinite rejection (e.g. claim 28: "said first parent protein) for antecedent basis would have been overcome by applicant's proposed amendment.

6. Indefinite rejection (e.g. claim 28: "to one another" and "compatible reactive groups...") upon further consideration is hereby withdrawn in view of applicant's arguments.

7. Indefinite rejection (e.g. claim 28: "having a C-terminus and an N-terminus") for redundancy is hereby retained. Applicant's argument that redundant or inherent language does not render the claim indefinite is not convincing since the inherent feature in the present instance does produce some confusion in light of the claim's prior use of the same language for the peptide segments.

8. Rejection of claims 28-36 under 35 USC 112, first paragraph for lacking *"possession* of the claimed invention". Applicant's arguments with regard to this rejection were considered but deemed nonpersuasive for the following reasons. Applicant argues that the specification clearly *enables* the ability to combine modules from the same or different proteins.

In this regard, applicant is referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the resulting "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is first noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co*

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

However, it is clear that applicant has not presented an adequate sample to demonstrate possession of the presently claimed invention. See *University of California v. Eli Lilly and Co.* U.S. Court of Appeals Federal Circuit (CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding adequate disclosure, the analysis of which does not address the absence or presence of undue experimentation.

As pointed out in the rejection of record, the specification discloses only limited examples that are neither representative of the claimed genus (which is not limited by peptide length or amino acid composition nor types of derivations), nor is it clear that they represent a substantial portion of the claimed genus. This showing clearly does not provide an adequate representation regarding the myriad possible peptides of different length which lack a common core which would be expected to elicit a common activity.

9. Anticipation rejection of claims 28-31 over the Cannes reference is hereby maintained. As pointed out by the Examiner , the reference clearly teaches chemical ligation (e.g. by thioesterification) of an amino terminus of one peptide (derived from a first (parent) protein) to a carboxyl terminus of a different peptide fragment (e.g. derived from a second (parent) protein). The claims would encompass both the instance where the parent proteins are same or different.

10. Anticipation rejection of claims 28-31 over the Dawson reference. Applicant's arguments were considered but not deemed persuasive for the following reasons.

Applicant's argument that the presently claimed invention represents the ligation of fragments from two *different* proteins is not convincing since the claims encompass the ligation of different functional domains from the same "protein" . Additionally in light of the unduly broad specification definition of "protein" (e.g. see specification page 7 "two or more covalent bound peptides; a peptide containing two or more amino acids), the domains present in the same overall protein, present in different regions of the same protein could nevertheless be deemed to originate from different proteins; since these separate fragments (of four or more amino acids) which comprise these domains represent different proteins within the specification definition of this term.

Applicant points to Fig. 2 as representing the ligation of peptides derived from the same protein. However, the reference clearly discloses that this is merely a representative example of the reference teaching and thus does not limit the teaching to ligating peptide segments present (or derived) from the same protein (e.g. IL-8).

Applicant argues that note 4 which involves the ligation of two pentapeptides; fails to specifically teach the origin (e.g. from the same or different proteins) of the individual peptides. However, it is clear that from the reference description of this footnote (E.g. on page 776) that the reference was teaching the applicability of the chemical ligation of "small peptides" in general regardless of source (e.g. from the same or different proteins). In this regard it is additionally noted that the reference further acknowledges the use of its techniques to form "backbone modified proteins, including *analogs* of protein domains" (e.g. see page 776: emphasis provided) which would encompass ligated fragments in which one or more fragement is not present (e.g. derived) from the same protein.. Accordingly, the combined teaching of the reference to one of ordinary skill in the art would be its general applicability for chemical ligation of peptide sequences from the same or different proteins (e.g. the formation of "analogues"). Thus applicant has failed to address the reference teaching as a whole to one of ordinary skill in the art. The Examiner also notes the failure of the presently claimed invention to specifically limit the protein or proteins from which the ligated fragments are to be "derived" and the means of derivation. Accordingly, the ligation of different pentapeptides which may be comprised in different prior art proteins would be sufficient to anticipate the present invention which broadly encompasses any means of derivation from any "protein" (e.g. any tetrapeptide or greater polypeptide).

Applicant's argument that the Gaertner reference fails to teach the ligation of different peptide segments *from different proteins* is not convincing for any of the following reasons:

a. Applicant's claimed invention is not limited to different proteins as argued;

b. One of the ligated fragments e.g. Ser-Leu-Leu is a peptide sequence which is clearly present in more than one different protein; to the extent that the claims encompass derivation from different proteins.

Applicant's argument that the Clark-Lewis reference fails to teach *ligation* was considered but deemed nonpersuasive for the following reasons. The reference undisputably teaches the "chemical syntheses" of "analog proteins" which comprise different "functional protein modules" (e.g. an IL-8 region and an IP-10 region) "derived" from "different proteins (e.g.IL-8 and IP-10) and thus constitute a "cross-over protein" within the scope of the present invention. The reference further teaches (e.g. page 16076) that the "chemical syntheses" encompasses solid phase protection/deprotection (e.g. t-boc) protocol which clearly constitutes *ligation* of N-terminal and C-terminal peptide segments having "compatible reactive groups" since a covalent bond is effected between an amino and carboxyl terminus of two different fragments.

Applicant argues that both the Cwirla et al. and Sticht et al. reference methods fail to teach "ligation" of functional domains. However, the presently claimed invention would encompass both recombinant and non-recombinant means of achieving ligation which results in "cross over proteins". For example, the Cwirla reference clearly discloses a method of producing libraries (e.g. collections) of "cross over proteins" by phage display in which the proteins are fused (e.g. ligated) proteins comprising different hexapeptides (e.g. a "functional protein module" as broadly defined on specification page 7 which is "derived" from a first protein) and phage proteins (e.g. a second "functional module" (e.g. pIII) "derived "from a phage protein). Similarly,

the production a recombinant library of clones which comprise chimeras (e.g. fusion or ligated proteins) comprising two different peptide segments as disclosed by Sticht would anticipate the presently claimed invention as broadly claimed.

Applicant's arguments regarding the double patenting rejections of record are not found persuasive for the reasons of record e.g. as expressed in the prior office action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

September 6, 2001

BENNETT CELSA
PRIMARY EXAMINER